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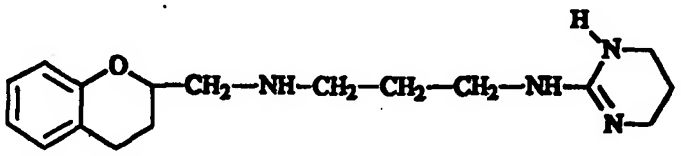
(54) Title: STARCH MICROSPHERE ANTI MIGRAINE COMPOSITION

(57) Abstract

The present invention relates to a powdery pharmaceutical composition comprising an anti migraine compound of formula (I) and starch microspheres, which is particularly suited for intranasal administration.



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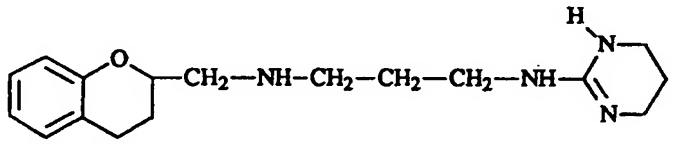
STARCH MICROSPHERE ANTI MIGRAINE COMPOSITION

The present invention relates to a powdery pharmaceutical composition comprising an anti migraine compound of formula (I) and starch microspheres, which is particularly suited for intranasal administration. The present invention further pertains to a process of preparing such pharmaceutical compositions as well as the use thereof as an anti migraine medicament.

WO 93/17017, published on September 2, 1993, discloses compounds of formula (I), the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof having selective vasoconstrictive properties.



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Among the compounds of formula (I), (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)-methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine and the pharmaceutically acceptable acid addition salts thereof were indicated as the preferred compounds.

In vitro and *in vivo* animal experiments have demonstrated that N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine possesses high and selective vasoconstrictory properties. The generic name for N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine is alniditan. The arterial vasoconstrictor response arises through agonistic activation of 5-HT_1-like receptors. Since excessive cerebral vasodilatation plays a role in migraine, N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine has an acute effect in migraine by virtue of its vasoconstrictor effects on cerebral arteries.

Pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example,

hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

Preferred acid addition salt form is the hydrochloride, especially the dihydrochloride.

Although in general, oral administration of a drug is considered as most convenient, this route poses particular problems when administering a drug, more in particular an anti-migraine drug, to patients suffering from a migraine attack. Migraine patients often feel nauseous, sometimes resulting in violent vomiting, thus hampering the oral administration of the anti-migraine drug. The successful oral delivery of some anti-migraine substances may also be impeded by its susceptibility to degradation by the acid environment of the stomach and by the digestive activity of several enzymes in the gastrointestinal tract. Other disadvantages of the oral route may be the often poor absorption due to gastroparesis and the extensive first-pass elimination in the liver (the hepatic first-pass effect), whereby a compound is transformed in the liver into a metabolite more prone to excretion. Along with convenient administration, it is essential for an effective treatment of a migraine attack that the activity of the drug sets on immediately, or at least very rapidly, after administration. Hence a means of directly inserting the drug into the bloodstream would be appropriate for the administration of an anti-migraine drug. An obvious way of doing so is by injecting a solution of the drug either intravenously, intramuscularly or subcutaneously. However, the consequent pain, risk of infection, the complex procedures of self-administration and potential for low patient compliance make such parenteral administration undesirable.

The anti migraine compounds of formula (I) are poorly absorbed and are prone for hepatic first-pass effect.

Intranasal administration appears to be an attractive alternative because it avoids gastro-intestinal degradation and the hepatic first-pass effect and it allows for convenient and

simple self-administration. However, the person skilled in the art of pharmaceutical formulations is faced with the problem of preparing a pharmaceutical composition which allows intranasal administration of a compound of formula (I) while maintaining the activity of the active ingredient. Furthermore high bioavailability, a rapid onset, and a lack of adverse side-effects due to intranasal administration are required of said composition. Moreover the person skilled in the art of pharmaceutical formulations is more and more confronted with requirements of registration authorities and quality control.

It was found that the pharmaceutical composition of the present invention comprising a therapeutically effective amount of a compound of formula (I) loaded on starch microspheres provides a solution to the problem of providing a intranasal pharmaceutical composition which meets the above described requirements.

WO 87/03197, published on June 4, 1987, describes pharmaceutical compositions comprising microspheres incorporating sodium cromoglycate, wherein the microspheres include material having ion-exchange properties. WO 89/03207, published on April 20, 1989, teaches drug delivery compositions comprising a plurality of microspheres, for instance starch microspheres, suitable for delivery of peptides across a mucosal surface.

The pharmaceutical composition subject to the present invention differs from the prior art in that it encompasses a pharmaceutical composition comprising starch microspheres and the anti migraine compound of formula (I) (not being a peptide and not being sodium cromoglycate), which pharmaceutical composition has a release profile which is suitable to bring expedient relief to anti-migraine patients.

Different types of starch can be used to prepare the microspheres, such as amylodextrin, amylopectin, hydroxyethylstarch, hydroxypropylstarch and the like. Preferred type of starch is 100 % amylodextrin. Microspheres of amylodextrin are available from Perstorp as Eldexomer.

At least 80 % (measured by weight) of the microspheres should have a diameter ranging between about 10 and 200 μm.

In an interesting embodiment of the present invention more than 90 % (measured by weight) of the microspheres should have a diameter between 10 and 200 μm.

In a more interesting embodiment of the present invention more than 80 % (measured by weight) of the microspheres should have a diameter ranging between about 53 and 106 µm.

In a preferred embodiment of the present invention more than 90 % (measured by weight) of the microspheres should have a diameter ranging between about 53 and 106 µm.

Absorption enhancers may be present. Absorption enhancers include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the (mucosal) cell membranes.

Preferably the pharmaceutical composition is substantially free of absorption enhancer.

The loading of the microspheres is also an important feature of the pharmaceutical composition of the present invention. The ratio of the amount of active ingredient over starch ranges between 0.01 and 0.8 (w/w), interestingly said ratio varies between 0.05 and 0.5 (w/w). Preferably the ratio between the amount of active ingredient over starch should be about 0.1 (w/w). In other words the concentration of active ingredient ranges from about 1 % (w/w) to about 44 % (w/w), interestingly from about 5 % (w/w) to 33 % (w/w) and preferably about 9 % (w/w).

The microspheres are suitably administered in the form of a freeze-dried powder.

The pharmaceutical composition subject to the present invention has an acceptable stability, hence an acceptable shelf-life when stored in an appropriate way. The term acceptable shelf-life refers to about 6 months.

The pharmaceutical composition according to the present invention may be prepared by dissolving a certain amount of the active ingredient in water and suspending in said solution the appropriate amount of starch, for example amylodextrin, mixing said suspension during a certain period in time and subsequently freeze-drying said suspension.

The powdery pharmaceutical composition should be prepared in such a reproducible way so that it allows a reproducible administration of the pharmaceutical composition. This implies, amongst others, good rheological properties of the powder.

An important requirement of intranasal administration of pharmaceutical compositions is the tolerability of such pharmaceutical compositions. Both local tolerability (lack of nasal irritation, throat irritation, dry nose, runny nose, taste and smell disturbances) as well as

overall tolerability must be absent or at least be in an acceptable range. Although tolerability is a subjective factor, it can be measured by pooling enough subjects in the clinical trials.

The pharmaceutical composition subject to the present invention delivers the drug in such a way that peak plasma levels are rapidly attained thus assuring a rapid onset which is required in the treatment of a migraine attack.

Another advantage of the present invention is that after the peak plasma level which is reached rapidly, the active ingredient is released over an extended period of time, thus providing a form of sustained effect. Migraine patients often suffer of recurrence headaches after initial good response, which requires at least a second administration of an anti-migraine drug. Depending upon the loading of the pharmaceutical composition of the present invention it is possible to maintain the plasma-levels at a therapeutic level over an extended period of time, and to delay or prevent recurrences from occurring.

The release profile of the pharmaceutical composition of the present invention is less likely to elicit adverse side effects which would be associated with higher plasma levels.

The microspheres can be administered via the nasal route using a nasal insufflator device or pressurized aerosol canister. These types of devices for nasal administration are art-known.

A further aspect of the invention provides a method of treating subjects having migraine by administering the pharmaceutical composition subject to the present invention to said subjects.

Experimental part.

Example 1

An amount of 330 mg of active ingredient was weighed into a 25 ml volumetric flask. The active ingredient was dissolved in Ultrapure water and Ultrapure water was added ad 25 ml. An amount of 3195 mg of Eldexomer microspheres was mixed with 188 ml of Ultrapure water by stirring during 30 minutes. The solution of active ingredient and the suspension of Eldexomer microspheres were mixed in a beaker. A magnetic stirrer was added. The beaker was covered with Parafilm, was placed on a stirrer and the contents was gently mixed. After mixing for 30 minutes the beaker was removed from the stirrer and the resulting suspension was divided between two conical flasks. The flask contents

was frozen by immersing the flask in liquid nitrogen while swirling. The flasks are subsequently transferred to an Edwards Modulyo freeze drier and freeze-dried during 67.4 hours.

98 % of the microspheres prepared in the above manner had a size ranging between 53 and 106 µm.

Example 2 : Clinical trial

Before each drug administration, subjects had taken breakfast. The trial medication was administered between 8 and 9 a.m. into the left nostril with the subject sitting in upright position. Subjects were asked to attempt not to sneeze and not to blow the nose following administration of the dose. The intake of coffee, tea or another drink within 2 hours after the nasal administration was forbidden. Thereafter, subjects were allowed to resume their usual diet. Alcoholic beverages were not allowed between 24 hours before and 24 hours after drug dosing.

The Eldexomer medication was supplied to the investigator as gelatin capsules containing starch (Eldexomer) micropheres comprising 2 mg of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride. The dosage was given as a single nasal administration into the left nostril : 2 mg of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride.

For administration of the Eldexomer microsphere powder formulation the Rynacrom nasal insufflator was used.

Venous blood samples (5 ml) were taken from an antecubital vein immediately before and at 5, 10, 15, 20, 30 and 45 minutes and at 1, 2, 4, 6, 8 and 24 hours after nasal administration. Blood samples were collected in heparinized tubes and were centrifuged for 10 minutes at 2500 rpm (1000 g) within 2 hours after collection. Separated plasma was aspirated with a disposable glass Pasteur pipette and transferred in 5 ml plastic tubes. The tubes were stoppered by means of polyethylene stoppers, and labelled with the investigator's name, trial number, subject's randomization number and subject's initials, date and time of sampling. Samples were stored at -20°C until assayed. Concentrations of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride in plasma were determined by radio immunoassay.

Tolerability

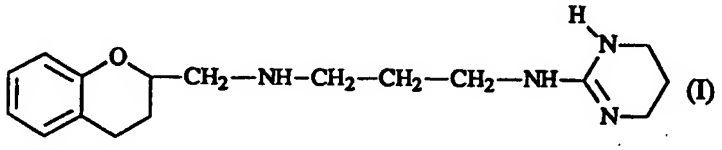
Both local nasal and overall tolerability were assessed during this trial. Local tolerability (nasal irritation, throat irritation, dry nose, sticky nose, runny nose, taste and smell disturbances) were rated by the subject immediately before and at 5, 10, 20, 30, 60 and 120 minutes after trial drug administration by means of a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). In addition, overall tolerability evaluation was based on adverse event reports. Volunteers were instructed to report all adverse events or any discomfort they experience during the course of the trial, with mention of time of onset, duration, severity and frequency.

Based on the individual plasma concentration-time data, the appropriate pharmacokinetic parameters, C_{max}, (peak plasma concentration), T_{max} (time to reach the peak plasma concentrations), $AUC_{0-\infty}$ and AUC_{0-t} (area under the plasma concentration-time curve up to the last time (t) with a measurable plasma concentration), $T_{1/2}$ (half-life of elimination) of (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride were determined.

The above mentioned composition showed a release profile appropriate for anti migraine treatment and the composition was found to be very tolerable. In comparison with a aqueous solution of the active ingredient, the present formulation resulted in a C_{max} that is about 4 times the C_{max} obtained with an aqueous solution and the $AUC_{0-\infty}$ obtained with the present formulation was more than 1.5 times that of the $AUC_{0-\infty}$ obtained with an aqueous solution.

Claims.

1. A powdery pharmaceutical composition comprising starch microspheres and a compound of formula (I),



(I)

a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof.

2. A pharmaceutical composition according to claim 1 wherein the compound is (-)-(R)-N-[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-N'-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride.

3. A pharmaceutical composition according to claims 1 or 2 wherein the starch used is amylodextrin.

4. A pharmaceutical composition according to claims 1 or 2 wherein the pharmaceutical composition is substantially free of absorption enhancers.

5. A pharmaceutical composition according to claims 3 or 4 wherein at least 80 % of the microspheres (measured by weight) have a size ranging from about 10 to 200 μm.

6. A pharmaceutical composition according to claim 5 wherein at least 80 % of the microspheres (measured by weight) have a size ranging from about 53 and 106 μm.

7. A process for preparing pharmaceutical compositions as claimed in claims 1 to 6 wherein the starch is mixed with the active ingredient and subsequently freeze-dried.

8. Use of a pharmaceutical composition as claimed in claims 1 to 6 for the manufacture of a medicament for treating migraine and related disorders.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 96/02345

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/505 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 17017 A (JANSSEN PHARMACEUTICA N.V.) 2 September 1993 cited in the application see page 45; examples 26,27 ---	1,2,4,8
A	AMERICAN PHARMACEUTICAL ASSOCIATION / PHARMACEUTICAL SOCIETY OF GREAT BRITAIN: "Handbook of Pharmaceutical Excipients" 1988 , AMERICAN PHARMACEUTICAL ASSOCIATION , WASHINGTON XP002014996 153140 see page 289, column 2, paragraph 9. ---	1
A	WO 93 02712 A (DANBIOSK UK LIMITED) 18 February 1993 see page 12, line 10 - line 13 see page 13, line 16 - line 17 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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3 October 1996	17. 10. 96

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Information on patent family members

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